QUANTITATIVE DIFFUSION-WEIGHTED IMAGING IN CANCER APPLICATIONS

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Dedicated to Mom, Dad,
Aravind, Anil

Certificate

This is to certify that the work contained in this thesis titled **"Quantitative Diffusion-weighted Imaging in Cancer Applications"** is a bonafide record of the work done at Indian Institute of Technology, Delhi by **Archana Vadiraj Malagi** (2017BMZ8358) for the award of **Doctor of Philosophy** in Biomedical Engineering. The work in this thesis was conducted under our supervision and guidance. The matter submitted in this thesis has not been submitted elsewhere for the award of any other degree.

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Archana Vadiraj Malagi

Abstract

Quantitative magnetic resonance imaging (MRI) quantifies multiple factors utilizing tissue-specific physical units. These quantitative metrics are sensitive to physiological tissue changes and pathologies. In recent years, demand for non-contrast quantitative MRI has grown, such as intravoxel incoherent motion combined with diffusion kurtosis imaging (IVIM-DKI). IVIM-DKI is a diffusion-weighted imaging technique that uses low-to-high diffusion sensitizing gradient strengths (b-value). IVIM-DKI doesn't require contrast agents, ensuring application safety to a wide variety of patients and reducing MRI costs. Although IVIM-DKI is beneficial for clinical studies, it has not yet been widely used in routine clinical practices because of a few technical problems: (i) the signal-to-noise ratio (SNR) of the IVIM-DKI signal is poor, (ii) piecewise simultaneous fitting of parameters result in noisy and unreliable parameter maps, (iii) the diagnostic utility of IVIM-DKI in a various clinical setting at different MRI field strength has not been proven, and (iv) the absence of a standardized protocol for organ-specific imaging leads to prolonged scan times. Thus, this thesis aims to address some of these challenges by proposing novel strategies for improving IVIM-DKI parametric map estimation using parametric reconstruction method validation of the novel model at different MRI field strengths and optimization of b-values for protocol standardization, which can promote the role of IVIM-DKI in the improved quantitative lesion characterization technique in cancer applications.

The first objective was to develop a novel strategy to improve the parameter estimation of IVIM-DKI for producing high-quality parametric maps. To implement this objective, the total three-dimensional total variation (TV) penalty function was utilized in conjunction with non-linear lease square optimization (NLLS) of the IVIM-DKI model (IDTV model). TV is an image-based reconstruction approach that corrects for NLLS error and adaptively removes any abrupt changes in the map while preserving the edges. Two models were implemented for the estimation of diffusion coefficient (D), perfusion coefficient (D*), perfusion fraction (f), and kurtosis (k) using either: (1) standard model and (2) IDTV model. Experimental simulation results showed accurate and high-quality IVIM-DKI parameter maps, particularly at low signal-to-noise ratios in simulations. Additionally, TV regularization was resilient to changes in SNR, resulting in less error and bias in IVIM-DKI parameter maps.

The second objective was to examine the clinical usefulness of IVIM-DKI analysis using the IDTV model in prostate mass characterization at different MRI field strengths (1.5T and 3T). The IDTV model resulted in enhanced parameter estimation with minimal error at 1.5T and 3T. Furthermore, compared to the standard model at 3T, the IDTV model at 1.5T resulted in lower parameter estimate error and higher-quality parametric reconstruction. D, f, and k estimated with the IDTV model showed higher diagnostic performance than the standard model. Hence, IVIM-DKI might play an essential role in prostate lesion diagnosis when paired with the IDTV model.

The third objective was to assess the efficacy of IVIM-DKI analysis with the IDTV model and machine learning-based multi-parametric texture analysis in characterizing pancreatic masses. Perfusion fraction was found to out-perform the diffusion measures (ADC and D) in discriminating pancreatic adenocarcinoma (PDAC) from the pancreatic neuroendocrine

tumor (pNET). Whole-volumetric texture analysis of individual or combination IVIM-DKI parameters with machine learning-based classification of pancreatic masses can help with the non-invasive characterization of pancreatic lesions.

The fourth objective was to optimize the b-value for IVIM and IVIM-DKI analyses by combining different b-values. IVIM and IVIM-DKI signals were modeled utilizing the IVIM model with the TV method (BE+TV model) and the IDTV model, respectively. The experimental findings of simulation and clinical data demonstrated that the BE+TV and IDTV models were resistant to b-value combinations. Furthermore, both models were robust to any number and combination of b-values, and they improved the quality of all parametric maps at low SNR. The BE+TV approach significantly enhanced the quality of D and f maps. The IDTV model, on the other hand, improved the quality of D, f, and k maps. The acquisition of IVIM and IVIM-DKI with optimal 8 b-values may be employed for faster acquisition times and high-quality parameter maps with comparable accuracy as 13b-values using the standard model with less acquisition time.

Finally, this thesis concluded by using an IVIM-DKI model with an optimized b-value for diagnosing malignant lymph nodes compared to fluorodeoxyglucose-positron emission tomography with computed tomography (FDG-PET/CT) imaging. The preliminary findings revealed that the IDTV model outperformed PET imaging in identifying benign and malignant lymph nodes in lymphoma and further classifying lymphoma subtypes. In diagnosing malignant lymph nodes, IVIM-DKI parameters showed higher diagnostic performance than ADC and PET parameters. IVIM-DKI can potentially be used for lymph node evaluation in lymphoma and is comparable to PET imaging.

सार

मात्रात्मक चुंबकीय अनुनाद इमेजिंग (एमआरआई) ऊतक-विशिष्ट भौतिक इकाइयों का उपयोग करने वाले कई कारकों को मापता है। ये मात्रात्मक मेट्रिक्स शारीरिक ऊतक परिवर्तन और रोग विकृति के प्रति संवेदनशील हैं। हाल के वर्षों में, गैर-विपरीत मात्रात्मक एमआरआई की मांग बढ़ी है, जैसे कि प्रसार कर्टोसिस इमेजिंग (आईवीआईएम-डीकेआई) के साथ संयुक्त इंट्रावॉक्सेल असंगत गति। आईवीआईएम-डीकेआई एक डिफ्यूजन-वेटेड इमेजिंग तकनीक है जो लो-टू-हाई डिफ्यूजन सेंसिटाइजिंग ग्रेडिएंट स्ट्रेंथ (बी-वैल्यू) का उपयोग करती है। आईवीआईएम-डीकेआई को कंट्रास्ट एजेंटों की आवश्यकता नहीं है, जो विभिन्न प्रकार के रोगियों के लिए आवेदन सुरक्षा सुनिश्चित करते हैं और एमआरआई लागत को कम करते हैं। हालांकि आईवीआईएम-डीकेआई नैदानिक अध्ययनों के लिए फायदेमंद है, लेकिन कुछ महत्वपूर्ण तकनीकी समस्याओं के कारण इसे अभी तक नियमित नैदानिक प्रथाओं में व्यापक रूप से उपयोग नहीं किया गया है: (i) आईवीआईएम-डीकेआई सिग्नल का सिग्नल-टू-शोर अनुपात (एसएनआर) खराब है। , (ii) मापदंडों की एक साथ फिटिंग से शोर और अविश्वसनीय पैरामीटर मानचित्र उत्पन्न होते हैं, (iii) विभिन्न एमआरआई क्षेत्र की ताकत पर विभिन्न नैदानिक सेटिंग में आईवीआईएम-डीकेआई की नैदानिक उपयोगिता, और (iv) अंग के लिए एक मानकीकृत प्रोटोकॉल की अनुपस्थिति- विशिष्ट इमेजिंग लंबे समय तक स्कैन समय की ओर ले जाती है। इस प्रकार, इस थीसिस का उद्देश्य आईवीआईएम-डीकेआई पैरामीट्रिक मानचित्र अनुमान में सुधार के लिए नई रणनीतियों का प्रस्ताव करके इन चुनौतियों का समाधान करना है, जो विभिन्न

एमआरआई क्षेत्र की ताकत पर उपन्यास मॉडल के पैरामीट्रिक पुनर्निर्माण विधि सत्यापन और प्रोटोकॉल मानकीकरण के लिए बी-वैल्यू के अनुकूलन का उपयोग कर सकते हैं, जो बढ़ावा दे सकते हैं कैंसर अनुप्रयोगों में बेहतर मात्रात्मक घाव लक्षण वर्णन तकनीक में आईवीआईएम-डीकेआई की भूमिका।

पहला उद्देश्य उच्च गुणवत्ता वाले पैरामीट्रिक मानचित्रों के निर्माण के लिए आईवीआईएम-डीकेआई के पैरामीटर अनुमान में सुधार के लिए एक नई रणनीति विकसित करना था। इस उद्देश्य को लागू करने के लिए, आईवीआईएम-डीकेआई मॉडल (आईडीटीवी मॉडल) के नॉन-लीनियर लीज स्क्वायर ऑप्टिमाइज़ेशन (एनएलएलएस) के संयोजन के साथ त्रि-आयामी टोटल टोटल वेरिएशन (टीवी) पेनल्टी फ़ंक्शन का उपयोग किया गया था। टीवी एक छवि-आधारित पुनर्निर्माण दृष्टिकोण है जो एनएलएलएस त्रुटि के लिए सुधार करता है और किनारों को संरक्षित करते हुए मानचित्र में किसी भी अचानक परिवर्तन को अनुकूल रूप से हटा देता है। प्रसार गुणांक (डी), छिड़काव गुणांक (डी *), छिड़काव अंश (एफ), और कर्टोसिस (के): (1) मानक मॉडल और (2) आईडीटीवी मॉडल के आकलन के लिए दो मॉडल लागू किए गए थे। प्रायोगिक सिमुलेशन परिणामों ने सटीक और उच्च-गुणवत्ता वाले आईवीआईएम-डीकेआई पैरामीटर मानचित्र दिखाए, विशेष रूप से सिमुलेशन में कम सिग्नल-टू-शोर अनुपात पर। इसके अतिरिक्त, टीवी नियमितीकरण एसएनआर में परिवर्तन के लिए लचीला था, जिसके परिणामस्वरूप आईवीआईएम-डीकेआई पैरामीटर मानचित्रों में कम त्रुटि और पूर्वाग्रह था।

दूसरा उद्देश्य विभिन्न एमआरआई क्षेत्र शक्तियों (1.5 टेस्ला और 3 टेस्ला) में प्रोस्टेट मास लक्षण वर्णन में आईडीटीवी मॉडल का उपयोग करके आईवीआईएम-डीकेआई विश्लेषण की नैदानिक उपयोगिता की जांच करना था। आईडीटीवी मॉडल ने 1.5 टेस्ला और 3 टेस्ला पर न्यूनतम त्रुटि के साथ पैरामीटर अनुमान बढ़ाया। इसके अलावा, 3 टेस्ला पर मानक मॉडल की तुलना में, 1.5 टेस्ला पर आईडीटीवी मॉडल के परिणामस्वरूप कम पैरामीटर अनुमान त्रुटि और उच्च गुणवत्ता वाला पैरामीट्रिक पुनर्निर्माण

हुआ। आईडीटीवी मॉडल के साथ अनुमानित डी, एफ और के ने मानक मॉडल की तुलना में उच्च नैदानिक प्रदर्शन दिखाया। इसलिए, आईडीटीवी मॉडल के साथ जोड़े जाने पर आईवीआईएम-डीकेआई प्रोस्टेट घाव के निदान में एक आवश्यक भूमिका निभा सकता है।

तीसरा उद्देश्य आईडीटीवी मॉडल और मशीन लर्निंग-आधारित बहु-पैरामीट्रिक बनावट विश्लेषण के साथ आईवीआईएम-डीकेआई विश्लेषण की प्रभावकारिता का आकलन करना था। अग्नाशयी न्यूरोएंडोक्राइन ट्यूमर (पीएनईटी) से विभेदक अग्नाशयी एडेनोकार्सिनोमा (पीडीएसी) में प्रसार उपायों (एडीसी और डी) को बाहर करने के लिए छिड़काव अंश पाया गया था। अग्नाशयी द्रव्यमान के मशीन लर्निंग-आधारित वर्गीकरण के साथ व्यक्तिगत या संयोजन आईवीआईएम-डीकेआई मापदंडों का संपूर्ण-वॉल्यूमेट्रिक बनावट विश्लेषण अग्नाशय के घावों के गैर-आक्रामक लक्षण वर्णन में मदद कर सकता है।

चौथा उद्देश्य विभिन्न बी-मानों को मिलाकर आईवीआईएम और आईवीआईएम-डीकेआई विश्लेषणों के लिए बी-वैल्यू का अनुकूलन करना था। आईवीआईएम और आईवीआईएम-डीकेआई सिग्नलिंग का विश्लेषण आईवीआईएम मॉडल का उपयोग करके क्रमशः टीवी विधि (बीई+टीवी मॉडल) और आईडीटीवी मॉडल के साथ किया गया था। सिमुलेशन और क्लिनिकल डेटा के प्रयोगात्मक निष्कर्षों ने प्रदर्शित किया कि बीई+टीवी और आईडीटीवी मॉडल बी-वैल्यू संयोजनों के प्रतिरोधी थे। इसके अलावा, दोनों मॉडल किसी भी संख्या और बी-मानों के संयोजन के लिए मजबूत थे, और उन्होंने कम एसएनआर पर सभी पैरामीट्रिक मानचित्रों की गुणवत्ता में सुधार किया। बीई + टीवी दृष्टिकोण ने डी और एफ मानचित्रों की गुणवत्ता में काफी वृद्धि की है। दूसरी ओर, आईडीटीवी मॉडल ने डी, एफ और के मानचित्रों की गुणवत्ता में सुधार किया। इष्टतम 8 बी-मानों के साथ आईवीआईएम और आईवीआईएम-डीकेआई के अधिग्रहण को कम अधिग्रहण समय के साथ मानक मॉडल का उपयोग

करते हुए 13 बी-मानों के रूप में तुलनीय सटीकता के साथ तेजी से अधिग्रहण के समय और उच्च गुणवत्ता वाले पैरामीटर मानचित्रों के लिए नियोजित किया जा सकता है।

अंत में, मानक एफडीजी-पीईटी/सीटी इमेजिंग की तुलना में घातक लिम्फ नोड्स के निदान के लिए एक अनुकूलित बी-मान के साथ आईवीआईएम-डीकेआई मॉडल का उपयोग करके इस थीसिस का निष्कर्ष निकाला गया। प्रारंभिक निष्कर्षों से पता चला है कि आईडीटीवी मॉडल ने लिम्फोमा में सौम्य और घातक लिम्फ नोड्स की पहचान करने और लिम्फोमा उपप्रकारों को वर्गीकृत करने में पीईटी इमेजिंग से बेहतर प्रदर्शन किया। घातक लिम्फ नोड्स के निदान में, आईवीआईएम-डीकेआई मापदंडों ने एडीसी और पीईटी मापदंडों की तुलना में उच्च नैदानिक प्रदर्शन दिखाया। आईवीआईएम-डीकेआई संभावित रूप से लिम्फोमा में लिम्फ नोड मूल्यांकन के लिए इस्तेमाल किया जा सकता है और पीईटी इमेजिंग के बराबर है।

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Glossary

DWI	Diffusion-weighted imaging
PCa	Prostate cancer
TRUS	Transrectal ultrasonography
MRI	Magnetic resonance imaging
CT	Computed tomography
FDG-PET/CT	Fluorodeoxyglucose-Positron emission tomography/CT
ADC	Apparent diffusion coefficient
IVIM	Intra-voxel incoherent motion
ME	Monoexponential
BE	Biexponential
DKI	Diffusion kurtosis imaging
IVIM-DKI	IVIM combined with DKI
SNR	Signal-to-noise ratio
2D	Two-dimensional
TV	Total variation
BE+TV	BE model with TV method
3D	Three-dimensional
BPH	Benign prostatic hyperplasia
AIIMS	All India Institute of Medical Sciences
EPI	Echo planar imaging
PI-RADS	Prostate Imaging Reporting & Data System
SE	Spin Echo
TR	Repetition time
TE	Time of echo
SSFP	Steady-state free precession
FS	Fat-supressed
TSE	Turbo SE
MRCP	Magnetic resonance cholangiopancreatography
HASTE	Half-Fourier Acquisition Single-shot Turbo spin Echo imaging
SE-EPI	Spin echo-echo planar imaging

SPIR	Spectral presaturation with inversion recovery
MFCP	Mass-forming chronic pancreatitis
SPEN	Solid papillary epithelial neoplasm
PDAC	Pancreatic adenocarcinoma
pNET	Pancreatic neuroendocrine tumor
FNAC	Fine-needle aspiration cytology
NMR	Nuclear magnetic resonance
RF	Radiofrequency
1D	One-dimensional
GRE	Gradient echo
FSE	Fast spin echo
PGSE	Pulsed gradient spin echo
ADC	Apparent diffusion coefficient
DDC	Distributed diffusion coefficient
MCP	Microcirculatory perfusion
D	Diffusion coefficient
D*	Pseudo-diffusion coefficient
f	Perfusion fraction
k	Kurtosis
CV	Coefficient of variation
wCV	Within-subject CV
RRMSE	Relative root means square error
RB	Relative bias
SD	Standard deviation
Pz	Peripheral zone
Tz	Transition zone
AFS	Anterior fibromuscular stroma
DCE	Dynamic contrast-enhanced
mp-MRI	Multiparametric-MRI
bp-MRI	Biparametric-MRI
AUC	Area under curve
ROC	Receiver-operating-characteristics
GS	Gleason score

AIP	Autoimmune pancreatitis
HL	Hodgkin lymphoma
NHL	Non-Hodgkin lymphoma
MIP	Maximum intensity projection
DLBCL	Diffuse large B-cell lymphoma
MALT	Mucosa-associated lymphoid tissue
CLL/SLL	Chronic lymphocytic leukemia/small lymphocytic lymphoma
HNSCC	Head and neck squamous cell carcinomas
NAC	Neo-adjuvant chemotherapy
NPC	Nasopharyngeal carcinoma
MRMR	Minimum Redundancy Maximum Relevance Algorithm
LASSO	Least absolute shrinkage and selection operator
GLCM	Gray-level co-occurrence matrix
NGTDM	Neighbourhood gray-tone difference matrix
GLRLM	Gray-level run length matrix
IDTV	IVIM-DKI model with TV method
SSIM	Structural similarity index
CV_{comb}	Combined CV
ANOVA	Analysis of variance
ANN	Artificial neural network
LOA	Limit of agreement